TSE Control in Tissue Donor Screening and Tissue Processing

Melissa A. Greenwald, MD

Division of Human Tissues

Office of Cellular, Tissue and Gene Therapies

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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100 YEARS 1902 2002 BIOLOGICS CONTROL ACT

Today's talk will focus on:

Specific areas of FDA tissue regulations pertaining to TSE Control

- **Registration Rule**
- **Donor Eligibility**
  - **Donor Eligibility Rule**
  - **CJD/vCJD Draft Guidance**
- **Current Good Tissue Practices Rule**

Abbreviations

- DE = Donor Eligibility
- RCDAD = Relevant Communicable Disease Agent or Disease
- HIV = Human Immunodeficiency Virus
- HBV = Hepatitis B Virus
- HCV = Hepatitis C Virus
- HTLV = Human T-lymphotrophic virus
- CMV = Cytomegalovirus
- §= Section (of the rule) ex. §1271.3
- PI = Package Insert
- CJD = Creutzfeldt-Jakob disease (vCJD=variant)

Regulatory Framework

- For Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), a risk-based, tiered approach proposed in 1997; FDA regulatory oversight commensurate with risk
- Focus--Prevent introduction, transmission and spread of communicable disease by all HCT/Ps
- However, for those HCT/Ps that are highly processed, used for other than their normal function, combined with other articles, or that have systemic effects on the body, must also demonstrate clinical *safety and efficacy* in addition to preventing introduction, transmission or spread of communicable disease

Effective Dates of the 3 Rules

- **Establishment registration and listing final rule**
  - **Published 1/19/01 (part 1271, subparts A and B)**
  - **Effective for all HCT/P establishments (except dura mater and heart valves) 1/21/03**
  - **Interim Rule postponed effective date to 1/23/04, with compliance date of 3/29/04 (except dura mater/valves)**
  - **Effective for dura mater and heart valves 5/25/05**
- **Donor eligibility final rule**
  - **Published 5/25/04 (part 1271, subpart C)**
  - **Effective 5/25/05 (concurrent with CGTP final rule)**
- **CGTP final rule;**
  - **Published 11/24/04 (part 1271, subparts D, E, F)**
  - **Effective 5/25/05**

What is Included?

Human Cells, Tissues and Cellular and Tissue-based Products (HCT/Ps)

- Musculoskeletal tissue (e.g., bone, ligament, tendon, fascia)
- Skin
- Ocular tissue (e.g., cornea, sclera)
- Human heart valves
- **Human dura mater**
- **Reproductive cells/tissue:**
  - **Subparts D (GTPs) and E (Reporting and Labeling) are not being finalized**
- **Hematopoietic stem cells (from peripheral and cord blood)**
- **Cellular therapies**
- **Cell/device and other combination therapies**

What is not included?

- **Vascularized organs**
- **Minimally manipulated bone marrow**
- **Xenotransplantation products**
- **Blood and blood products**
- **Secreted or extracted products; e.g., human milk, collagen, cell factors**
- **Ancillary products used in manufacture**
- ***In vitro* diagnostic products**

Registration

- **Establishments must register who perform any manufacturing functions:**
  - **Recovery**
  - **Donor screening or testing**
  - **Processing**
  - **Storage**
  - **Distribution**

Registration

- **Registered banks who list dura mater as a product include:**
  - **IOP, Inc. in Costa Mesa CA**
  - **PM Medical, Inc. in Ft. Lauderdale FL**
  - **SSI – Spinal Solutions, Inc. in Dallas TX**
  - **University of Miami Tissue Bank in FL**

Donor Eligibility Rule

- **A donor eligibility determination must be performed by a responsible person who determines and documents the eligibility of the donor**
- **Donor is eligible if free from risk factors for or clinical evidence of relevant communicable diseases, free from risks associated with xenotransplantation, and tests negative or nonreactive**

Donor Eligibility Rule

- **All donors must be screened**
- **Review the relevant medical records for**
  - **Risk factors for, and clinical evidence of RCDADs**
  - **Communicable disease risks associated with xenotransplantation**
- **Relevant medical records includes a current donor medical history interview, physical assessment or exam, and other available records**

Donor Eligibility Rule

- **Donors not tested for TSEs because there are no FDA-licensed, cleared, or approved tests**
- **All donors must be tested, both general and specific testing requirements**
- **§ 1271.85(e) for donors of dura mater--there must be an adequate assessment designed to detect evidence of TSE**
- **The assessment includes, after removal of the dura mater, a full brain autopsy of the donor, including gross and histological examination, performed by a qualified neuropathologist, to identify evidence of TSE changes**

DE Rule - RCDADs

- **For all HCT/Ps**
  - **HIV, types 1 and 2**
  - **HBV**
  - **HCV**
  - **Human TSE, including CJD and vCJD**
  - **Treponema pallidum (agent of syphilis)**
- **For viable, leukocyte-rich HCT/Ps**
  - **HTLV, types I and II**
- **For reproductive HCT/Ps**
  - **Chlamydia trachomatis**
  - **Neisseria gonorrhea**

DE Rule - RCDADs

- In addition, FDA is adding the following as RCDADs under § 1271.3(r)(2) through the guidance process:
  - **West Nile Virus**
  - **Sepsis**
  - **Vaccinia (Smallpox vaccination)**
  - **Severe Acute Respiratory Syndrome (SARS)**

Donor Eligibility

- **In order to maintain flexibility and remain current in knowledge and technology, FDA makes specific recommendations for donor screening and testing through guidance**
- **Draft guidances published for**
  - **CJD/vCJD (June 2002)**
  - **Donor Eligibility (May 2004)**
- **These guidances will be published as one final guidance; anticipate publication soon**

CJD/vCJD draft guidance

- **Deferral of tissue donors for risk factors for “classic” (sporadic) CJD—already recommended in the 1997 guidance for industry**
- **The draft guidance for CJD/vCJD (6/2002) incorporated those deferrals, and in addition recommends deferrals for risk factors for variant CJD—travel or residence in BSE-affected countries**
- **There was a 6 month comment period**

CJD/vCJD draft guidance

- **Draft guidance was modeled after the guidance for industry for blood donors, published August 2001**
- **Recommends the same countries, dates, and lengths of travel/residence as does the guidance for blood donors**
- **Permits an exception for the collection and storage of hematopoietic stem cells from donors who live in or travel to a BSE-affected country (for urgent medical need because of HLA-matching issues)**

CJD/vCJD draft guidance

- **Comments reviewed at CBER**
- **Final recommendations for CJD/vCJD screening will be incorporated into the final Donor Eligibility guidance when published**

CJD/vCJD draft guidance

- **Specific deferral criteria in the draft guidance are an indication of FDA's current thinking about how to adequately and appropriately reduce the risk of infectious disease transmission by this agent**
- **Until a final guidance is issued, establishments would not necessarily have to "adopt" the recommended deferral criteria but the regulations do require some screening for TSEs (including CJD and vCJD)**

CJD/vCJD draft guidance

- **May use alternate screening criteria as long as the screening criteria are at least as strict as those recommended by FDA (i.e., are as effective to adequately and appropriately reduce the risk of infectious disease transmission)**
- **No testing recommendations made—there are no FDA licensed, cleared, or approved donor screening tests**

CJD/vCJD Risks for Donor Screening

- **Persons who have been diagnosed with vCJD or any other form of CJD**
- **Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the CNS or other neurological disease of unknown etiology**

Donor Screening (cont.)

- **Persons who are at increased risk for CJD**
  - **Receipt of human dura mater transplant**
  - **Receipt of human pituitary-derived growth hormone**
  - **One or more blood relatives diagnosed with CJD**
- **Persons who spent three months or more cumulatively in the U.K. from the beginning of 1980 through the end of 1996**

Donor Screening (cont.)

- **Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe for 6 months or more from 1980 through 1990, or elsewhere in Europe for 6 months or more from 1980 through 1996**

Donor Screening (cont.)

- **Persons who lived cumulatively for 5 years or more in Europe between 1980 and the present**
- **Persons who received any transfusion of blood or blood components in the U.K. between 1980 and the present**
- **NOTE—If the person being interviewed is not familiar with the term CJD, you may take that as a negative response**

The UK

- **For the guidance, the UK includes**
  - **England**
  - **Northern Ireland**
  - **Scotland**
  - **Wales**
  - **Isle of Man**
  - **Channel Islands**
  - **Gibraltar**
  - **the Falkland Islands**

Military Bases

- **In Northern Europe includes**
  - **Germany, UK, Belgium, Netherlands**
  - **Deferral from 1980-1990**
- **In Southern Europe includes**
  - **Greece, Turkey, Spain, Portugal, Italy**
  - **Deferral from 1980-1996**

Family History of CJD

- **Would be ineligible UNLESS:**
  - **the diagnosis of CJD was subsequently found to be an incorrect diagnosis;**
  - **the CJD was iatrogenic; or**
  - **laboratory testing (gene sequencing) shows that the donor does not have a mutation associated with familial CJD**

CGTP--General

- **Methods used in, and facilities and controls used for manufacture of HCT/Ps**
- **Narrower in scope than GMPs (GTPs focus on prevention of communicable disease transmission; prevention of contamination/cross-contamination)**
- **Broad goals applicable to the wide range of HCT/Ps**
- **Establishments have the flexibility to determine how to meet goals through their SOPs**

Requirements

- Exemptions and Alternatives
- Quality Program
- Personnel
- Procedures
- Facilities
- Environmental Control and Monitoring
- Equipment
- Supplies/Reagents
- Recovery

Requirements

- Processing and Process Controls
- Process Changes
- Process Validation
- Labeling Controls
- Storage
- Receipt, Pre-Distribution Shipment, Distribution
- Records
- Tracking
- Complaint File

A few specifics related to cGTPs

- **Pooling of donor tissues is prohibited**
- **Dura mater must be processed using any published validated process that reduces the risk of TSEs, unless following the process adversely affects the clinical utility of the dura mater**
- **Any published validated processes that are used must be verified in each establishment**

A few specifics related to cGTPs

- **Establishments must archive appropriate specimens from each dura mater donor, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of TSE, and to enable appropriate disposition of any affected nonadministered dura mater tissue, if necessary**
- **Records must be kept for 10 years including records for archived specimens of dura mater**

cGTP Guidance

- **FDA will develop a cGTP draft guidance document (none currently).**
- **Dura mater is transferred to CBER from CDRH as of effective date of DE and GTP rules (25 May 2005)**
- **We will look at the CDRH guidance on submission of 510(k)s for dura mater and transfer some of these recommendations into the draft GTP guidance.**

For further information

http://www.fda.gov/cber/gdlns/cjdvcjd0602.htm

http://www.fda.gov/cber/tissue/docs.htm

Melissa Greenwald

301-827-2002

melissa.greenwald@fda.hhs.gov